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# The effect of therapies on the quality of life of patients with systemic lupus erythematosus: a meta-analysis of randomized trials

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## Abstract

**Introduction:** Systemic lupus erythematosus (SLE) is a multi-systemic, chronic inflammatory disease of autoimmune nature, which can impair performance in daily life activities, causing to a compromised quality of life. Thus, the aim of this study was to evaluate the effect of therapies, such as physical activity, cognitive behavioral therapy, pharmacological treatment and phytotherapy in the quality of life of patients with systemic lupus erythematosus.

**Materials and methods:** A systematic review with a meta-analysis of randomized clinical trials was conducted by searching the PubMed database, including studies comparing patients who participated in cognitive therapy, physical activity, pharmacological treatment or phytotherapeutic treatment.

**Results:** Of the seven studies included in this meta-analysis, a significant difference was observed in the quality of life of patients with lupus who participated in the intervention groups compared to the control groups (– 10.27 95% CI: – 15, 77 at – 4.77,  $p = 0.0003$ ,  $I^2 = 0\%$ ).

**Conclusion:** Interventions improve the Quality of life of patients with SLE. However, the methodological quality of the included articles and the sizes of the samples for being small propose that new randomized clinical trials be performed.

**Keywords:** Systemic lupus erythematosus, Quality of life, Meta-analysis

## Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multisystemic inflammatory disease that can cause skin lesions, inflammation of the joints and membranes that cover the lungs and heart, nephritis, cardiovascular, hematological, gastrointestinal and neuropsychiatric disorders. In this way, the symptoms can appear slowly and progressively or quickly and vary with phases of activity and remission [1], which may impair performance in daily activities, leading to impairment of quality of life (QoL).

Since the World Health Organization advocates that QoL reflects on individuals' perceptions that their needs are being met, or that they are being denied opportunities

to achieve happiness and self-realization, regardless of their physical state of health or social and economic conditions [2], therapies and/or treatments are used for these patients, in order to minimize the implications imposed by the disease and improve the quality of life. Randomized clinical trials (RCTs) that demonstrated the effects of these therapies and/or treatments on the health aspect in general, reported an improvement in quality of life [3, 4]. However, the studies have relatively small samples.

Because of the greater statistical power, a systematic review with meta-analysis of randomized clinical trials may provide more accurate estimates of the efficacy of the intervention than individual trials. A RCT meta-analysis was performed comparing patients who were part of the intervention group (cognitive therapy, physical activity, pharmacological and phytotherapeutic treatment) with control groups, in order to identify if the

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interventions provided statistically significant improvements in QoL. Thus, the objective of this study was to evaluate the effect of therapies, such as physical activity, cognitive behavioral therapy, pharmacological treatment and phytotherapy, and identify whether interventions provide statistically significant improvements on the quality of life of patients with systemic lupus erythematosus.

## Methodology

A systematic review with a meta-analysis of randomized clinical trials was performed, observing the criteria defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

### Eligibility criteria

Randomized clinical trials evaluating the quality of life of patients with SLE were included. We included studies comparing patients who participated in cognitive therapy, physical activity, pharmacological treatment or phytotherapeutic treatment. To carry out such a study, the PubMed database was consulted. The search was not restricted by language. The publications were selected if they reported on quality of life in patients with SLE and specified the use of a quality of life scale.

The exclusion criteria were studies that included children, those who did not specify the general health domain of the patient, the studies that reported only baseline measurements, those who did not clearly identify the presence of a control group and those who did not provide standard deviation nor confidence interval.

### Search

In the PubMed search strategy, keywords were used according to their description in MeSH, the complete search strategy was: (((((((((Systemic Lupus Erythematosus) OR Lupus Erythematosus) OR Libman-Sacks Disseminatus) OR Disease, Libman-Sacks) OR Libman Sacks Disease) OR "lupus erythematosus, systemic"[MeSH Terms])) AND (((((Life Quality) OR Health-Related Quality Of Life) OR Health-Related Quality Of Life) OR HRQOL) OR ("quality of life"[MeSH Terms] OR quality of life [Text Word]))) AND (((clinical [Title/Abstract] AND trial [Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random\*[Title/Abstract] OR random allocation [MeSH Terms] OR therapeutic use [MeSH Subheading]))).

### Data collect

The relevant articles published in the period between 2010 and 2017 were initially selected by the screening of titles and abstracts, going to the stage of reading the articles in full, collected through database searches.

A previous exploratory reading of all the selected material was carried out, followed by a more selective and

analytical reading of the parts that really mattered. Subsequently, the information extracted from the articles (authors, title, journal, year, abstract and conclusions) was recorded in order to order and summarize the material, so as to enable the obtaining of information relevant to the research.

The process of identifying the methodological aspects and extracting the data of the articles was carried out by two independent reviewers. In the event of any disagreement between them, the article was read again in full for re-evaluation based on pre-determined eligibility criteria.

Subsequently, a meta-analysis was performed using Review Manager Analysis software (RevMan 5.3), from Cochrane Collaboration. The effects were summarized using differences between means with 95% confidence intervals, using a fixed effects model. Heterogeneity was assessed using the statistics  $I^2$ .

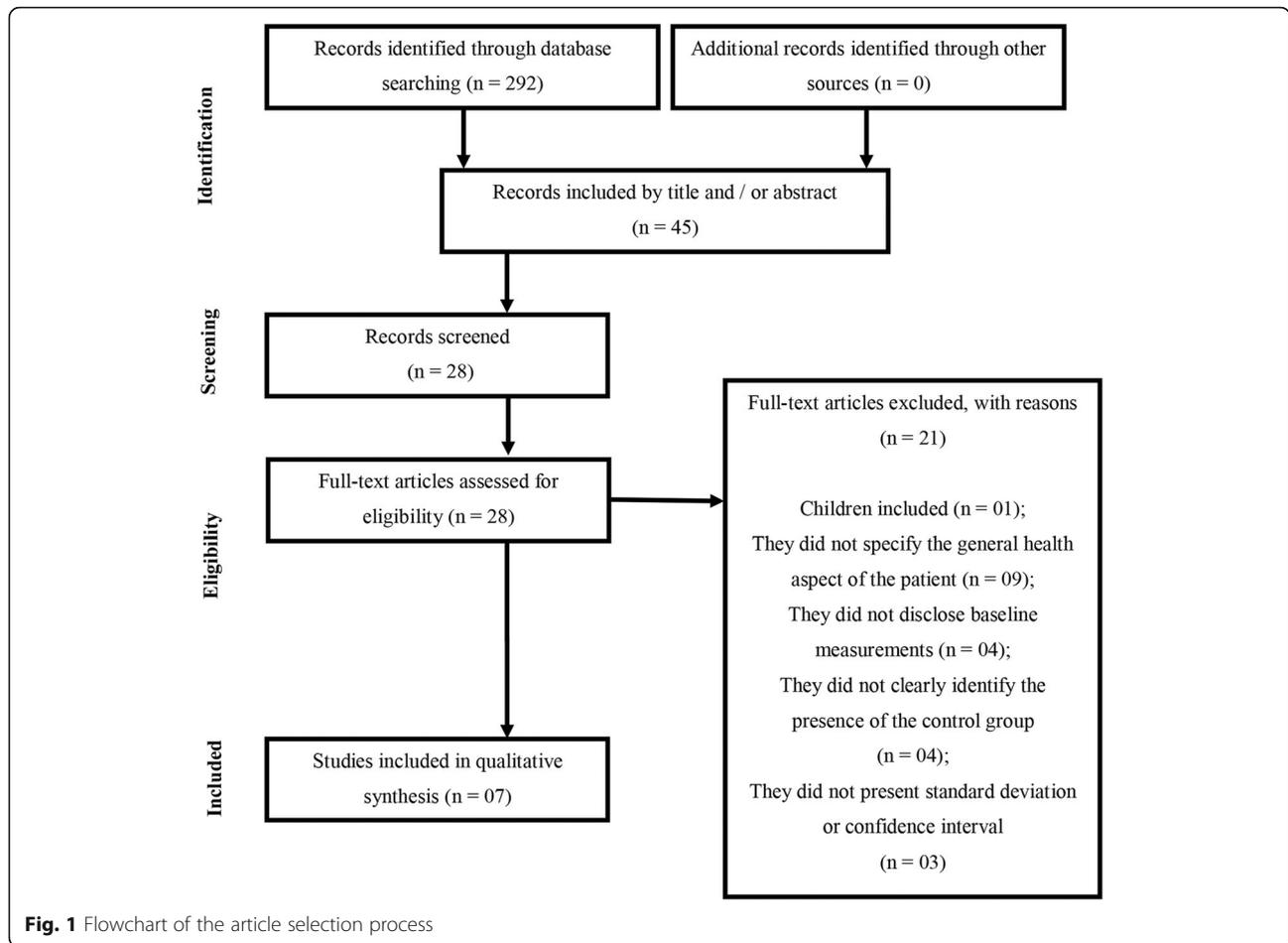
### Risk of Bias

To assess the risk of bias, we used the Cochrane Collaboration criterion, which evaluated the following domains: 1) sequence generation (randomization): We identified the method used to generate the random sequence, in order to evaluate if it was possible to produce comparable groups; 2) allocation concealment: We identified the method used to conceal the random sequence, in order to know if the allocation of the interventions could be predicted before or during the recruitment of the participants; 3) blindness of participants and blindness of professional: We analyzed whether there was an adequate description of the measures used to blind participants of the studies and professionals involved 4) Results Evaluator Blindness: We evaluated if the studies described the measures used to blind the evaluators of the outcome, in relation to the knowledge of the intervention provided to each participant; 5) incomplete follow-up data: We evaluated whether the studies reported loss of outcome data, whether losses were balanced between groups, as well as whether data were allocated in an appropriate way; 6) Report of selective outcome: We evaluated the possibility that the studies included in this review reported incomplete outcomes and 7) Other sources of bias: We judged this item considering the quality and extent of the information reported in the included studies.

## Results

The search strategy resulted in 292 articles, of which 28 studies were selected for a detailed reading. Of these, 07 studies met the eligibility criteria and were included in the present study. Figure 1 shows the flowchart of the studies included in this analysis and Table 1 summarizes the characteristics of these studies.

Two trials compared physical activity with usual care (total  $n = 73$ , of which 38 were in the physical activity



group); two trials compared cognitive behavioral therapy with conventional care (total  $n = 79$ , of which 39 were in the cognitive therapy group); two trials compared phytotherapeutic treatment with placebo (total 100, of which 50 were in the phytotherapeutic group); and one study compared pharmacological treatment with placebo (total  $n = 48$ , of which 11 were in the epratuzumab group).

**Risk of bias**

Of the studies that were included in the review, in the field of random sequence generation (randomization), 03 studies presented low risk of bias, 3 were not clear and 01 was not randomized. Only 01 study presented low risk of bias in the concealment domain of the allocation and 06 were not clear. Only 03 studies had low risk of bias of blind participants, 02 were not clear and 02 presented high risk of bias. Regarding the blindness of the evaluators, only 01 study presented low risk of bias, while 03 were uncertain and 03 had high risk of bias. In the 07 studies, losses in follow-up and exclusions were described. Regarding the selective reporting of outcome, 03 studies presented low risk of bias and 04 presented

high risk of bias. Only 01 study presented low risk of bias in the intention to treat domain, 03 were not clear and 03 presented high risk of bias (Fig. 2).

**Effects of interventions**

Of the seven studies included in this meta-analysis ( $n = 300$ ), a significant difference in quality of life was observed in SLE patients who participated in the intervention groups compared to the control groups (-10.27 95% CI: -15.77 to -4.77,  $p = 0.0003$ ,  $I^2 = 0\%$ ) (Fig. 3).

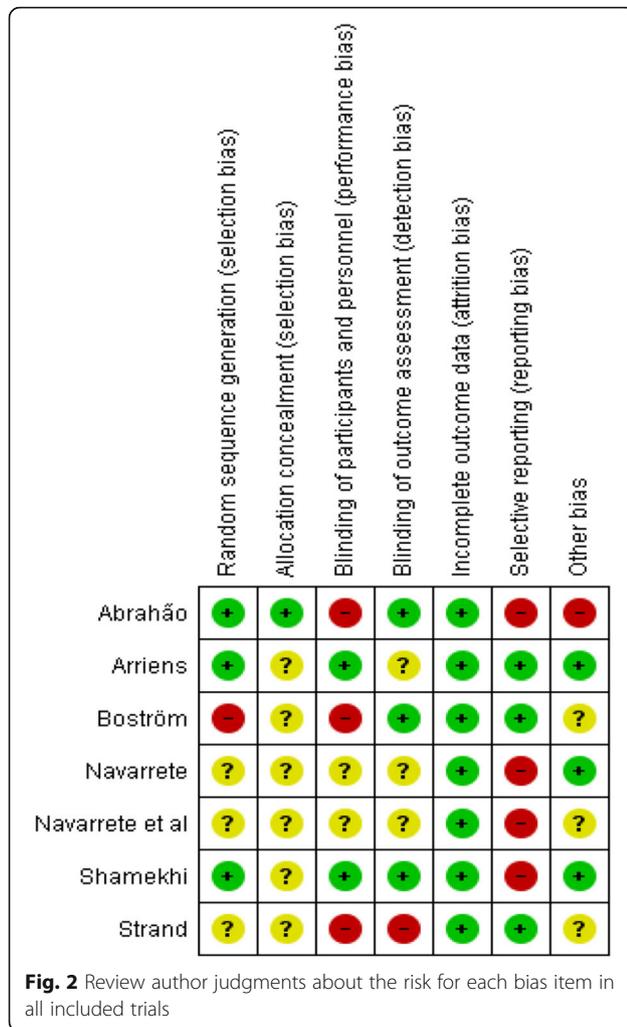
**Physical activity**

Two studies, Abrahão et al [5] and Boström et al [6] evaluated QOL ( $n = 73$ ). It was verified that the physical activity program provided a non-significant improvement in the QoL compared to the control groups (-6.46 95% CI: -19.85 to 6.93,  $p = 0.34$ ,  $I^2 = 0$ ) (Fig 4).

In this meta-analysis, Abrahão et al [5] and Boström et al [6], performed a physical activity program during 03 and 12 months, respectively, including patients who have SLE in a physical activity program, and had control groups that received only usual care, was observed that there was a significant difference in relation to physical

**Table 1** Characteristics of the studies included in the review

Author year	Population	Intervention	Follow-up	Outcome	Result
Abrahão, 2015 [6]	42	Intervention (n = 21) cardiovascular training Control group (n = 21) (usual care and information about the disease)	03 months	Quality of life	The intervention group presented a significant improvement in the physical health and vitality aspect, in the general health aspect no significant differences were found (SF36 health survey questionnaire)
Arriens, 2015 [9]	32	Intervention (n = 18) (supplementation with fish oil) Control group (n = 14) (placebo)	06 months	Quality of life	The intervention group presented a significant improvement in the mental health and vitality aspect (SF36 health survey questionnaire)
Boström, 2016 [7]	31	Intervention (n = 17) (physical activity) Control group (n = 14) (usual care)	12 months	Quality of life	The intervention group had improved mental health, there was no significant improvement in the general health aspect (SF36 health survey questionnaire).
Navarrete, 2010 [4]	45	Intervention (n = 21) (cognitive behavioral therapy) Control group (n = 24) (health care, moderate exercise, balanced diet and plenty of rest)	15 months	Quality of life	The intervention group had a significant reduction in the level of depression, anxiety and daily stress and a significant improvement in QoL and somatic symptoms (SF36 health survey questionnaire).
Navarrete et al, 2010 [8]	34	Intervention (n = 18) cognitive behavioral therapy Control group (n = 16) (usual care)	15 months	Quality of life	The intervention group presented improvement in the level of physical function, vitality, general health perception and mental health (SF36 health survey questionnaire).
Shamehki, 2017 [5]	68	Intervention (n = 32) (supplementation of green tea extract) Control group (n = 36) (placebo)	03 months	Quality of life	The intervention group presented a significant increase in vitality and general health (SF36 health survey questionnaire).
Strand, 2013 [10]	48	Intervention (n = 11) (epituzumab 720 mg/m2) Control group (n = 37) (placebo)	12 months	Quality of life	The intervention group showed evident improvements in the mean SF-36 scores (SF36 health survey questionnaire).



function (Fig. 4), but not to vitality (Fig. 5), but in general health the results were not statistically significant.

**Cognitive behavioral therapy (CBT)**

Navarrete et al [3, 7], assessed in two studies the QoL of patients with SLE who participated in cognitive behavioral therapy (n = 79). It was observed that the CBT

group provided a significant improvement in the QoL of these patients when compared to the control groups (-17.66 95% CI: -26.69 to -8.63, p = 0.0001, I<sup>2</sup> = 7%) (Additional file 1).

During 15 months, Navarrete et al [3, 7] performed a CBT program with SLE patients and the control groups received conventional care. It was shown that the group that performed CBT presented a reduction in the level of depression and anxiety, improvement in the level of physical function and vitality, as well as an improvement in the general perception of health and a statistically significant improvement in the QoL.

**Phytotherapeutic treatment**

Two studies, Arriens et al [8] and Shamekhi et al [4], evaluated QoL after treatment with herbal medicines (n = 100). It was observed that the phytotherapeutic treatment for QoL was not statistically significant when purchased from the placebo groups (-4.94 95% CI: -16.31 to 6.43), p = 0.39, I<sup>2</sup> = 0%) (Additional file 1).

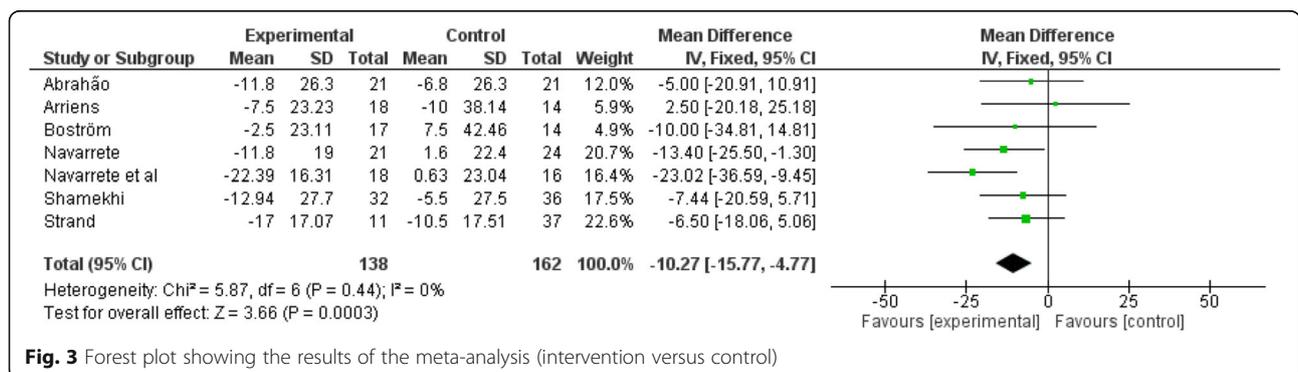
In this meta-analysis, Arriens et al [8] and Shamekhi et al [4] carried out a program with herbal medicines for a period of 06 and 03 months, respectively. It was observed that supplementation resulted in improvement in vitality and in the general health aspect of QoL.

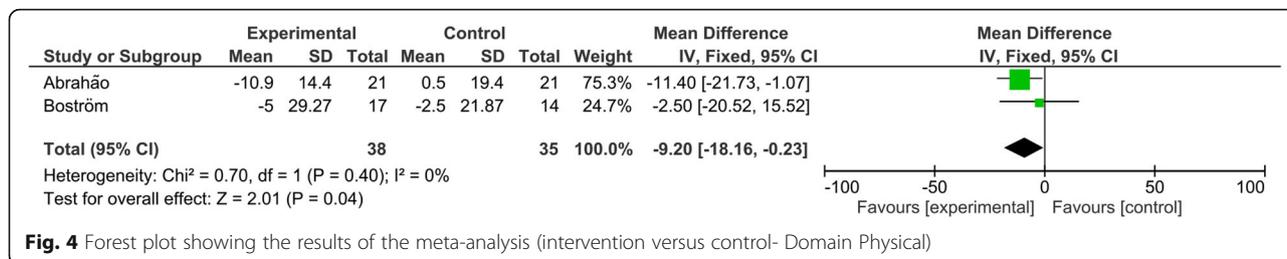
**Pharmacological treatment**

Strand et al [9] carried out a 12-month study (n = 48) comparing QoL in SLE patients who used epratuzumab compared to the placebo group. It was not possible to conduct a meta-analysis due to the fact that only one study met the eligibility criteria of this review. However, mean SF-36 scores showed evident improvements in the intervention group.

**Discussion**

In this systematic review, it was found that the treatments/therapies were associated with a statistically significant improvement in the QoL of patients with SLE. However, if observed separately, physical activity and phytotherapy programs did not achieve significant improvements. It is worth





**Fig. 4** Forest plot showing the results of the meta-analysis (intervention versus control- Domain Physical)

mentioning that it was not possible to perform the meta-analysis with the pharmacological treatment.

Patients with SLE may develop with limitations in exercise capacity and reduction in QoL [10], due to the great amount of pathophysiological and psychosocial symptoms imposed by the disease [11]. Regular physical exercise has as main objectives for SLE patients, increase the perception of physical function and reduce fatigue, besides providing numerous benefits for mental health, which directly interfere in the perception of QoL [12].

Abrahão et al [5] found higher SF-36 scores in physical aspects and vitality, however, no significant differences were found in the score referring to the general health aspect. The same was reported by Boström et al [6], who after 12 months, concluded an improvement in the mental health field and considered it a positive effect, since there were lower feelings of nervousness and depression. However, regarding the general health aspect of QoL, no significant results were obtained.

Behavioral cognitive therapies focus on the psychological aspect as a positive effect in the therapeutic approach in anxiety and mood disorders, depression and chronic pain. The purpose of CBTs is to minimize the interference of the disease in patients' daily lives, improving the social aspect and the independence levels and, consequently, the well-being of these individuals [13]. This was demonstrated by Navarrete et al [3, 7] in their studies, where they found a significant reduction in levels of depression, anxiety and daily stress, and at the same time, obtained improvements in levels of physical function, vitality, mental health and general health perception.

The results found by Navarrete et al [3, 7], suggest that CBT relieves somatic symptoms, facilitating coping with

the disease and improving the implications of long-term health behaviors.

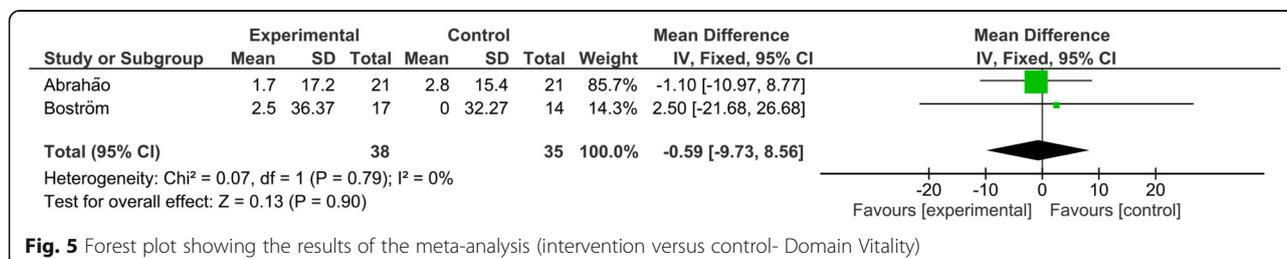
The phytotherapeutic treatment is used as a way to intervene in the health-disease process, aiming to establish a balance between innumerable dimensions that establish the human being, contributing to better well-being and QoL.

The changes in the perception of QoL refer to the greater capacity to perform activities and the achievement of satisfactory levels of health [14].

Arriens et al [8] presented in their study with fish oil an improvement in disease activity, inflammatory biomarkers and QoL. However, this improvement in QoL was not statistically significant, since most of the SF-36 scores remained unchanged. There has been an improvement in vitality and emotional well-being. This can be complemented by Shamekhi et al [4], who obtained results favorable to general health, physical appearance and vitality.

Pharmacological treatment for SLE has been shown to be essential, since patient survival has increased in the last two decades. However, QoL has decreased due to the fact that currently available treatments are often associated with adverse factors [15], leading to a reduction in physical well-being and a negative impact on daily living activities [16]. This is not consistent with the study by Strand et al [9].

The study lasted for 12 months and it was observed that the patients who were part of the intervention group (epratuzumab 720 mg/m<sup>2</sup>) exceeded the normative values in pain scores, social, emotional, mental health and vitality scores, and no improvement was identified in the general aspect of health.



**Fig. 5** Forest plot showing the results of the meta-analysis (intervention versus control- Domain Vitality)

This systematic review with meta-analysis has some limitations. First, this review was limited to only a single database. In addition, few studies were included and the studies included in this review consisted of small samples (between 31 and 68 participants), which may suggest the possibility of type II errors. We also believe that there may have been multiple publication bias for the subgroup of cognitive behavioral therapy, since part of the population may have been computed in two studies, which may compromise the results of the analysis for this subgroup. However, in order to avoid compromising the outcome of the meta-analysis in which we included all studies (fig. 06), we performed a new analysis in which we included only one study from Navarrete, and we identified that there was no statistically significant change (see Additional file 1).

The presence of bias in these studies leads to conclusions that systematically tend not to be completely reliable [17]. Only two studies clearly described the blinding of participants and practitioners and the confidentiality of concealment of allocation, and only three trials reported blinding of outcome assessors. However, as previously described, the analysis was hampered by the small number of studies and participants.

### Conclusion

This systematic review with meta-analysis suggests that interventions such as physical activity, cognitive behavioral therapy, phytotherapy, and pharmacological treatment improve QOL in patients with SLE, being more evident in cognitive behavioral therapy. However, the methodological quality of the included articles and the small sample sizes propose that new randomized clinical trials be performed. The studies should be elaborated with greater methodological rigor and a greater number of patients.

### Additional file

**Additional file 1: Figure S1.** Forest plot showing the results of the meta-analysis (One study was excluded) (TIF 10038 kb)

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### Authors' contributions

RRBTM; KL and TCH drafted the manuscript. RRBTM and TCH carried out the analysis. All authors read and approved the final manuscript.

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### Ethics approval and consent to participate

Not applicable.

### Consent for publication

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### Competing interests

The authors declare that they have no competing interests.

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### References

- Piga M, Congia M, Gabba A, Figus F, Floris A, Mathieu A, et al. Musculoskeletal manifestations as determinants of quality of life impairment in patients with systemic lupus erythematosus. *Sage J*. 2017.
- Pereira EF, Teixeira CS, Santos A. Qualidade de vida: abordagens, conceitos e avaliação. *Rev. Bras. Educ. Fis. Esporte*. 2012;26:241–50.
- Navarrete-Navarrete N, Peralta-Ramírez MI, Sabio-Sánchez JM, Coin MA, Robles-Ortega H, Hidalgo-Tenorio C, et al. Efficacy of cognitive Behavioural therapy for the treatment of chronic stress in patients with lupus erythematosus: a randomized controlled trial. *Psychother Psychosom*. 2010; 79:107–15.
- Shamekhi Z, Amani R, Habibagahi Z, Namjoyan F, Ghadiri A, Malehi AS. A Randomized, Double-blind, Placebo-controlled Clinical Trial Examining the Effects of Green Tea Extract on Systemic Lupus Erythematosus Disease Activity and Quality of Life. *Phytother Res*. 2017;31(7):1063–71.
- Abrahão MI, Gomiero AB, Peccin MS, Grande AJ, Trevisani VFM. Cardiovascular training vs. resistance training for improving quality of life and physical function in patients with systemic lupus erythematosus: a randomized controlled trial. *Scand J Rheumatol*. 2015;1–5.
- Boström C, Elfving B, Dupré B, Opava CH, Lundberg IE, Jansson E. Effects of a one-year physical activity programme for women with systemic lupus erythematosus – a randomized controlled study. *Sage Journals*. 2016;25: 602–16.
- Navarrete-Navarrete N, Peralta-Ramírez MI, Sabio JM, Martínez-Egea I, Santos-Ruiz A, Jiménez-Alonso J. Quality-of-life predictor factors in patients with SLE and their modification after cognitive behavioural therapy. *Sage Journals*. 2010;19:1632–9.
- Arriens C, Hynan LS, Lerman RH, Karp DR, Mohan C. Placebo-controlled randomized clinical trial of fish oil's impact on fatigue, quality of life, and disease activity in systemic lupus erythematosus. *Nutr J*. 2015;14:82.
- Strand V, Petri M, Kalunian K, Gordon C, Wallace DJ, Hobbs K, et al. Epratuzumab for patients with moderate to severe flaring SLE: health-related quality of life outcomes and corticosteroid use in the randomized controlled ALLEVIATE trials and extension study SL0006. *Rheumatology*. 2014;53:502–11.
- Carvalho MR, Sato EI, Tebexreni AS, Heidecher RT, Schenkman S, Neto TL. Effects of supervised cardiovascular training program on exercise tolerance, aerobic capacity, and quality of life in patients with systemic lupus erythematosus. *Rev Arthritis & Rheumatism*. 2005;53:838–44.
- Yuen HK, Cunningham MA. Optimal management of fatigue in patients with systemic lupus erythematosus. *Rev. Ther Clin Risk Manag*. 2014;10: 775–86.
- Mancuso CA, Perna M, Sargent AB, Salmon JE. Perceptions and measurements of physical activity in patients with systemic lupus erythematosus. *Sage Journals*. 2010;20:231–42.
- Solati K, Mousavi M, Kheiri S, Hasanpour-Dehkordi A. The effectiveness of mindfulness-based cognitive therapy on psychological symptoms and quality of life in systemic lupus erythematosus patients: a randomized controlled trial. *Oman Med J*. 2017;32:378–85.
- Loures MC, Porto CC, Siqueira KM, Barbosa MA, Medeiros M, Brasil WV, et al. Contribuições da fitoterapia para a qualidade de vida: percepções de seus usuários. *Rev. Enfermagem - UERJ*. 2010;18:278–83.
- Tian J, Luo Y, Wu H, et al. Risk of adverse events from different drugs for SLE: a systematic review and network meta-analysis. *Lupus Sci Med*. 2018;5: e000253. <https://doi.org/10.1136/lupus-2017-000253>.

16. Medeiros MM, Menezes AP, Silveira VA, Ferreira FN, Lima GR, Ciconelli RM. Health-related quality of life in patients with systemic lupus erythematosus and its relationship with cyclophosphamide pulse therapy. *Eur J Intern Med*. 2008;19:122–8.
17. Carvalho AP, Silva V, Grande AJ. Avaliação do risco de viés de ensaios clínicos randomizados pela ferramenta da colaboração Cochrane. *Diagn Tratamento*. 2013;18:38–44.

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